Section of Endocrinology

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The History of the Discovery of Addison's Disease

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THE PAPER TO THE SOUTH LONDON MEDICAL SOCIETY

A HUNDRED years ago, on Thursday, March 15, 1849, Dr. Addison, at the request of the President, John Hilton, proceeded to describe, before the South London Medical Society: "A remarkable form of anæmia, which, although incidentally noticed by various writers, had not attracted, as he thought, by any means the attention it really deserved. It was a state of general anæmia incident to adult males, and had for several years past been with him a subject of earnest inquiry and of deep interest. It usually occurs between the ages of 20 and 60; sometimes proceeding to an extreme degree in a few weeks, but more frequently commencing insidiously, and proceeding very slowly, so as to occupy a period of several weeks, or even months, before any very serious alarm is taken either by the patient or by the patient's friends. Its approach is first indicated by a certain amount of languor and restlessness, to which presently succeed a manifest paleness of the countenance, loss of muscular strength, general relaxation or feebleness of the whole frame, and indisposition to, or incapacity for, bodily or mental exertion. These symptoms go on increasing with greater or less rapidity: the face, lips, conjunctivæ, and external surface of the body, become more and more bloodless; the tongue appears pale and flabby; the heart's action gets exceedingly enfeebled, with a weak, soft, unusually large, but always strikingly compressible pulse; the appetite may or may not be lost; the patient experiences a distressing and increasing sense of helplessness and faintness; the heart is excited, or rendered tumultuous in its action, the breathing painfully hurried by the slightest exertion, whilst the whole surface bears some resemblance to a bad wax figure: the patient is no longer able to rise from his bed; slight œdema perhaps shows itself about the ankles; the feeling of faintness and weakness becomes extreme, and he dies either from sheer exhaustion, or death is preceded by signs of passive effusion or cerebral compression. In three cases only was there an inspection of the body after death, and *in all of them was found a diseased condition of the suprarenal capsules.* Dr. Addison inquired if it were possible for all this to be merely coincidental? It might be so, but he thought not, and making every allowance for the bias and prejudice inseparable from the hope or vanity of an original discovery, he confessed that he felt it very difficult to be persuaded that it was so. On the contrary, he could not help entertaining a very strong impression that these hitherto mysterious bodies—the suprarenal capsules—may be either directly or indirectly concerned in sanguification; and that a diseased condition of them, functional or structural, may interfere with the proper elaboration of the body generally, or of the red particles more especially. At all events, he considered that the time had arrived when he felt himself warranted in directing the attention of the profession to these curious facts."

THE 1855 MONOGRAPH

Little attention appears to have been paid to these observations, and it was six years before Addison himself again brought this condition to the notice of the medical profession by the publication of a short monograph "On the Constitutional and Local Effects of Disease of the Supra-renal Capsules" in the introduction to which he says: "There are still, however, certain organs of the body the actual functions and influence of which have hitherto entirely eluded the researches, and bid defiance to the united efforts of both physiologist and pathologist.

"Of these, not the least remarkable are the 'supra-renal capsules', the *atrabiliary* capsules of Caspar Bartholinus; and it is as a first and feeble step towards inquiry into the functions

and influence of these organs suggested by pathology, that I now put forth the following pages."

Every author who writes upon Addison's disease acknowledges that Addison's original description of the condition has not been improved upon either in respect of the accuracy and the thoroughness of his observations, or in the eloquence of his narrative. We shall do well therefore to browse for a few moments among the pages of what is undoubtedly one of the outstanding medical classics of the nineteenth century.

"It will hardly be disputed", it begins, "that at the present moment the functions of the supra-renal capsules, and the influence they exercise in the general economy, are almost or altogether unknown. The large supply of blood, which they receive from three separate sources; their numerous nerves, derived immediately from the semilunar ganglia and solar plexus; their early development in the fœtus; their unimpaired integrity to the latest period of life; and their peculiar gland-like structure—all point to the performance of some important office: nevertheless, beyond an ill-defined impression, founded on a consideration of their ultimate organization, that, in common with the spleen, thymus, and thyroid body, they in some way or other minister to the elaboration of the blood, I am not aware that any modern authority has ventured to assign to them any special function or influence whatever.

"To the physiologist and to the scientific anatomist, therefore, they continue to be objects of deep interest; and doubtless both the physiologist and anatomist will be inclined to welcome and regard with indulgence the smallest contribution calculated to open out any new source of inquiry respecting them. But if the obscurity which at present so entirely conceals from us the uses of these organs justify the feeblest attempt to add to our scanty stock of knowledge, it is not less true, on the other hand, that any one presuming to make such an attempt ought to take care that he do not, by hasty pretensions, or by partial and prejudiced observation, or by an over-statement of facts, incur the just rebuke of those possessing a sounder and more dispassionate judgment than himself.

"Under the influence of these considerations I have for a considerable period withheld, and now venture to publish, the few facts bearing upon the subject that have fallen within my own knowledge, believing, as I do now, that these concurring facts, in relation to each other, are not merely casual coincidences, but are such as admit of a fair and logical inference —an inference that, where these concurring facts are observed, we may pronounce with considerable confidence the existence of diseased supra-renal capsules.

"As a preface to my subject, it may not be altogether without interest or unprofitable to give a brief narrative of the circumstances and observations by which I have been led to my present convictions.

"For a long period I had from time to time met with a very remarkable form of general anæmia, occurring without any discoverable cause whatever—cases in which there had been no previous loss of blood, no exhausting diarrhœa, no chlorosis, no purpura, no renal, splenic, miasmatic, glandular, strumous, or malignant disease.

"Accordingly, in speaking of this form in clinical lecture, I perhaps with little propriety applied to it the term 'idiopathic' to distinguish it from cases in which there existed more or less evidence of some of the usual causes or concomitants of the anæmic state.

"It makes its approach in so slow and insidious a manner that the patient can hardly fix a date to his earliest feeling of that languor which is shortly to become so extreme. The countenance gets pale, the whites of the eyes become pearly, the general frame flabby rather than wasted; the pulse, perhaps large, but remarkably soft and compressible, and occasionally with a slight jerk, especially under the slightest excitement; there is an increasing indisposition to exertion, with an uncomfortable feeling of faintness or breathlessness on attempting it; the heart is readily made to palpitate; the whole surface of the body presents a blanched, smooth and waxy appearance; the lips, gums, and tongue seem bloodless; the flabbiness of the solids increases; the appetite fails; extreme languor and faintness supervene, breathlessness and palpitations being produced by the most trifling exertion or emotion; some slight œdema is probably perceived above the ankles; the debility becomes extreme. The patient can no longer rise from his bed, the mind occasionally wanders, he falls into a prostrate and half-torpid state, and at length expires. Nevertheless, to the very last, and after a sickness of, perhaps, several months' duration, the bulkiness of the general frame and the obesity often present a most striking contrast to the failure with exhaustion observable in every other respect.

"With perhaps a single exception the disease, in my own experience, resisted all remedial efforts, and sooner or later terminated fatally.

"It was whilst seeking in vain to throw some additional light upon this form of anæmia that I stumbled upon the curious facts which it is my more immediate object to make known to the profession; and however unimportant or unsatisfactory they may at first sight appear, I cannot but indulge the hope that, by attracting the attention and enlisting the co-operation

of the profession at large, they may lead to the subject being properly examined and sifted, and the inquiry so extended as to suggest, at least, some interesting physiological speculation, if not still more important practical indications.

"The leading and characteristic features of the morbid state to which I would direct attention are, anæmia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change of colour in the skin, occurring in connexion with a diseased condition of the 'supra-renal capsules'. We discover a most remarkable and, so far as I know, characteristic discoloration taking place in the skin —sufficiently marked, indeed, as generally to have attracted the attention of the patient himself or of the patient's friends.

" This discoloration pervades the whole surface of the body, but is commonly most strongly manifested on the face, neck, superior extremities, penis, and scrotum, and in the flexures of the axillæ and around the navel.

" It may be said to present a dingy or smoky appearance, or various tints or shades of deep amber or chestnut-brown; and in one instance the skin was so universally and so deeply darkened that but for the features the patient might have been mistaken for a mulatto.

"In some cases the discoloration occurs in patches, or perhaps rather certain parts are so much darker than others as to impart to the surface a mottled or somewhat chequered appearance; and in one instance there were, in the midst of this dark mottling, certain insular portions of the integument presenting a blanched or morbidly white appearance, either in consequence of these portions having remained altogether unaffected by the disease, and thereby contrasting strongly with the surrounding skin, or, as I believe, from an actual defect of colouring matter in these parts.

"This singular discoloration usually increases with the advance of the disease; the anæmia, langour, failure of appetite, and feebleness of the heart, become aggravated; a darkish streak usually appears on the commissure of the lips: the body wastes, but without the emaciation and dry, harsh condition of the surface, so commonly observed in ordinary malignant cases; the pulse becomes smaller and weaker; and without any special complaint of pain or uneasiness the patient at length gradually sinks and expires."

The State of Knowledge Concerning the Adrenal Glands Before 1849

Addison himself indicated, in the passages which I have just quoted from his monograph, that "the functions of the supra-renal capsules, are almost or altogether unknown". In the beautiful copperplates of human anatomy which Eustachius completed in 1552, but which were preserved in the Vatican Library until Pope Clement XI gave them to his physician Lancisi for publication in 1714, the adrenals are shown. Jean Riolan, bitter critic of William Harvey, named them the "supra-renal capsules" in 1629, though some years previously in Copenhagen, Caspar Bartholinus the elder, grandfather of that Caspar Bartholinus who described the vaginal glands, believed they contained black bile in their "cavity". A hundred years later the Académie des Sciences of Bordeaux offered a prize for an essay on "Quel est l'usage des glandes surrénales?" Apparently no one could put forward even a plausible theory, for the adjudicator recommended that the prize should not be awarded.

Another hundred years later in 1841, François Magendie, the physiological mentor of the great Claude Bernard, made the somewhat enigmatic remark that as no one believed any longer in black bile, the adrenals "had ceased to be secreting agents".

The comparatively large size of the organs in the fœtus had led to the suggestion that they were the fœtal kidneys, which ceased to have any function after birth.

Development of Knowledge of the Adrenals Subsequent to 1849

Addison's brilliant discovery was like a comet in a starless sky. It flashed across the scene and disappeared. Some people, especially in this country, even denied its existence. The prophet was not to be without honour, however, for Trousseau in 1856, the year after the publication of the monograph, named the condition "La maladie d'Addison" and that impetuous and ebullient figure Charles Edouard Brown-Séquard lost no time in collecting together fifty-one rabbits, eleven dogs, cats, mice and pigs, and depriving them of their adrenals, insisting when they all succumbed that they had died of Addison's disease and that the adrenal glands contained a life-preserving material. This, the first conception of an endocrine secretion, was looked upon with scepticism by some of Brown-Séquard's contemporaries, who were used to the sudden changes in his chequered career, and the wild ideas that chased each other through his impulsive mind, and they were inclined to attribute the death of his animals to more cynical causes.

From 1856, when Brown-Séquard performed his classical experiments, onwards for

nearly forty years nothing further was added to the knowledge of the adrenals. In 1894 Oliver and Schäfer demonstrated the presence of a pressor substance in the adrenal medulla. In 1901, Takamine and Aldrich independently isolated adrenaline in crystalline form, Aldrich giving it the empirical formula of $C_9H_{13}NO_3$; and in 1904 Stolz synthesized it. It thus became the first hormone to be chemically isolated, have its structure established and to be synthesized. In 1917 Rogoff and Stewart began the series of researches which established cortical extracts as possessing life-preserving properties. In 1919 Cannon propounded his "emergency" theory of adrenal medullary function. In 1928 Szent-Györgyi embarked upon his search for a powerful reducing agent in the adrenal cortex and ended up by discovering vitamin C. In 1930 Swingle and Pfiffner prepared a cortical extract which maintained life in adrenalectomized dogs and which was subsequently employed in the treatment of Addison's disease. In 1936 Kendall isolated corticosterone in crystalline form. In 1937 Reichstein prepared deoxycorticosterone acetate synthetically. In 1938 Simpson employed it in the treatment of Addison's disease. In 1946 17-hydroxy-11-dehydro-corticosterone (Kendall's Compound E) was prepared from deoxycholic acid by Sarrett, working at the Merck Research Laboratories, and in 1949, exactly one hundred years after Addison was addressing the South London Medical Society, Philip Hench, of the Mayo Clinic, made the startling announcement that Compound E or "cortisone" could completely relieve the symptoms of rheumatoid arthritis.

The Background of Addison's Discovery

Was Addison's discovery a lucky chance, or did he deserve the fame it has subsequently bestowed upon his name?

Undoubtedly the condition was not a new disease. Marañón, the great Spanish physician, endocrinologist and historian, has diagnosed in retrospect a case of Addison's disease in a priest at Escorial, the hamlet where Philip the Second was later to build in the shape of the grill on which St. Lawrence was martyred, that magnificent edifice, part monastery, part cathedral, part palace, in gratitude for the victory of St. Quentin. The monk's illness occurred in 1554, the year that Mary of England became Philip's wife.

Addison was lucky not to have been forestalled on at least five occasions. In his own hospital his senior colleague, the great Richard Bright, had, as early as 1831, observed and recorded a case of Addison's disease, and had preserved the adrenal glands which were tuberculous. Addison, in reporting on this case again, in his 1855 monograph, writes : "It does not appear that Dr. Bright either entertained a suspicion of the disease of the capsules before death, or was led at any period to associate the colour of the skin with the diseased condition of these organs, although his well-known sagacity induced him to suggest the probable existence of some internal malignant disease." In 1823, Schotte recorded a typical case, and Kirkes also described a case before Addison's monograph was published. In 1856 Sibley recorded another case at the Middlesex Hospital. In 1846, Aran published a series of cases of supposed pancreatic disease one of which is given in full detail and is clearly a case of Addison's disease. Aran, however, mistook the site of the abscess found on opening the abdomen at autopsy. The pus originated in the adrenal, but he thought it came from the pancreas.

Addison's achievement was in realizing that the adrenal disease was the cause of the clinical syndrome which he so vividly described, and the following considerations will show that this was no lucky coincidence.

(1) *Addison as a Dermatologist*

In the first place, Addison was especially intrigued by the pigmentation in this condition because he had a singular interest in skin disorders and might well have made a name and a fortune for himself as a dermatologist had he so wished. It is, however, one of the paradoxes of this fascinating story that the founder of clinical endocrinology abhored specialism in medicine. He had studied under Thomas Bateman, the disciple of Robert Willan, the founder of British dermatology, and the mantle of Bateman had fallen upon Addison's shoulders. He is the only person to have enjoyed the distinction of having three diseases called after him: Addison's anæmia, Addison's disease and Addison's keloid or localized scleroderma. He also gave the first description of xanthoma. During his many years of intimate association with Guy's Hospital he was responsible for building up the unique collection of wax models of skin conditions fashioned by Joseph Towne, the modeller, whom Astley Cooper introduced to Guy's and who served the hospital in this capacity for over fifty years. The famous marble bust of Thomas Addison, which Wilks thought to be such an excellent likeness, is by Towne.

(2) *Addison as Diagnostician*

Secondly, Addison was outstandingly famous as a diagnostician. To him the diagnosis of a patient's illness was a problem that must be solved, however long it took him to do so,

darting from one side of the bed to the other because he was deaf in one ear, and however much he might weary the patient or his student audience in the process. He had been known to return to the Hospital in the middle of the night, much to the astonishment of the ward sister, because just as he had got into bed he realized that he had forgotten to examine a patient he had seen in the afternoon, for a hernia. He was insistent on detailed and accurate recording of clinical observations, and introduced the systematic writing of ward clerk's reports at Guy's. He spent many hours in the dead house, trying to unravel the cause of death in some case the diagnosis of which had eluded him; and it must be remembered that in these days post-mortem examinations were the exception rather than the rule. His fame as a diagnostician made him one of the first "consulting physicians" as we understand the term to-day. The fashionable Victorian physician seldom had cases referred to him by a general practitioner or a colleague. His practice depended on the extent to which he was known to the public, and patients would call at his house and be herded into his waiting room on the off-chance of his being able to see them. Many fashionable physicians such as Gull resigned their hospital appointments comparatively early in life in order to devote more time to the profitable pursuit of their private practices. Gull, for instance, died worth £344,000.

Addison was not a physician of this type. He spent a considerable proportion of his time in the hospital, and though he was a man of forceful personality, who commanded the loyal and devoted respect of his students, he did not always completely satisfy the patient or his relatives, for he was too honest to think much about treatment, which at that time was practically non-existent. Nevertheless his opinion on diagnosis was sought constantly by his colleagues.

(3) *Addison in* 1849 *and* 1855

Addison's discovery was not due to the intuitive brilliance of youthful genius, but rather to the rigid discipline of the trained and mature observer. The monograph of 1855 was the last of his publications, and it is probable that neither he nor his most intimate friends appreciated that it would in time become one of the most famous contributions to medical literature. Indeed it is clear that his brief communication in 1849 to the South London Medical Society was made with diffidence, and would quite possibly never have been made at all but for John Hilton, his surgical colleague, and author of that great surgical classic "Rest and Pain". Addison allowed six years to elapse before elaborating the subject of his modest and unpretentious communication, and there seems little doubt that he would never have written the monograph, but for the diligent preparation of the material and the loyal, and diplomatic, encouragement of his friends and especially of a young man named Samuel Wilks, not yet on the Staff of Guy's.

Addison was anything but a prolific writer, and considering that he was the first to teach the clinical signs of fatty liver, to describe the symptoms and pathology of appendicitis, to demonstrate that pneumonia is due to an inflammatory exudate into the alveoli and not into the non-existent parenchyma of the lung, to demonstrate that phthisis is a mixed infection, that xanthoma is associated with jaundice, as well as describing pernicious anæmia and Addison's disease, the 13 papers which were collected together by Wilks and Daldy for publication by the New Sydenham Society, indicate a degree of literary restraint which might well be emulated by many less eminent and originally-minded writers.

Addison therefore was an old rather than a young man when he wrote his famous monograph. He was in fact 60, and Senior Physician to Guy's Hospital. His influence in the Hospital at this time was greater than that of any Guy's man, including Richard Bright, and except possibly Astley Cooper. He had always been a brilliant teacher. In his early days at Guy's he had earned £800 a year teaching students outside the Hospital Materia Medica. Sir William Hale-White, whose "Materia Medica" is still one of the most authoritative books on the subject, says: "He even made the dry bones of Materia Medica attractive."

He had devoted literally his entire life for the past thirty years to Guy's and the advancement of medicine. He was a bachelor up to the age of 52, and he had no hobbies or recreations, other than an annual visit to Lanercost in Cumberland from which his yeoman ancestry was derived.

Indeed his single-minded devotion to Guy's, his introspective and melancholic nature, and his extreme embarrassment when called upon to speak in public—he confessed that he used to shake with fright whenever he addressed the Guy's Physical Society, a mere student organization—prevented him from acquiring the marks of distinction which his more extroverted colleagues collected with ease. He was never President of the Royal College of Physicians; he was neither knighted nor did he become a baronet, like Gull, or Wilks after him, and Astley Cooper before him; he was not elected a Fellow of the Royal Society. He did, however, become President of the Medico-Chirurgical Society—now the Royal Society of Medicine.

His introspective and melancholic nature was the secret cross he had to bear. He did his

best to overcome it. Wilks, who knew him best, says he was an affable man. His students feared him, respected him and loved him. When he resigned from Guy's they asked him to come back, though he was 65 at that time. The last letter he ever wrote shows how much he appreciated their affection. "I can truly affirm", it says, "that I ever found my best support and encouragement in the generous gratitude and affectionate attachment, as well as my proudest reflections, in the honorable and most exemplary conduct of my pupils." He had been subject to fits of profound depression all his life. They had led him to rise from his bed of insomnia and pace the streets, where he occasionally met some colleague hastening home from a late call. To those who did not know him, these nocturnal pacings would be wrongly construed, and it was whispered that he sought the company of the ladies of the street. On many occasions he had contemplated suicide. In 1860 he retired from public life and from his beloved Guy's, because he thought his younger colleagues and particularly William Gull wanted to deprive him of his position. He went to live in Brighton and, though constantly guarded by two attendants, he succeeded in evading them and threw himself out of a window, to end a selfless though highly introspective life.

The Influence of "King" Harrison on Addison's Career

To turn for a moment to his early life. His appointment to the Staff of Guy's was yet another indication of the prescience of that autocratic personality who was one of the three men who have made Guy's Hospital. The first was Thomas Guy, a governor of St. Thomas's who saw the need to establish a hospital to care for the chronic sick and the insane. The last was Lord Nuffield, whose remarkable benefactions not only to Guy's but to Medicine as a whole have led us at Guy's to erect a statue to his honour during his lifetime. The third man was Benjamin Harrison, Treasurer of the hospital for fifty-one years, from 1797–1848. He was personally responsible for the appointment to the Hospital of Astley Cooper, Richard Bright, Thomas Addison, William Gull and Thomas Hodgkin. The case of Addison is especially noteworthy. Addison had obtained his M.D. in Edinburgh, and he came to Guy's five years later in 1820 as an ordinary student, but owing to the preferment exercised by "King" Harrison he was appointed to the staff in 1824. His only serious rival was Dr. Edward Seymour who had actually received a recommendation to the Governors from the future King William IV.

The Immediate Consequences of Addison's Monograph

In his communication to the South London Medical Society Addison was obviously describing pernicious anæmia, though some of the cases on which this paper was based were examples of Addison's disease. In the 1855 monograph, Addison had not altogether shed the idea of "idiopathic" anæmia, and had yet, on the other hand, gone too far by including cases of malignant disease of the adrenal glands. No one could easily mistake to-day, however, the classical description which he applied to the clinical condition which we now know as Addison's disease.

The monograph was not universally hailed with acclamation. Even twenty years later when Greenhow delivered his Croonian Lectures on Addison's disease he perceived a disinclination to accept the condition as a clinical entity. Papers were written in Germany and France in disproof of its existence. In England specimens were exhibited for years at the Societies, and discussions took place upon them before doubts ceased to be thrown upon the reality of the condition. Two or three papers read before the Medico-Chirurgical Society (now our Royal Society of Medicine) were not approved for publication, so that no record can be found in the *Transactions* of this remarkable discovery. Addison was deeply hurt at this as he had not long before been President of the Society. At Edinburgh, where Addison had obtained his M.D., Hughes Bennett and other professors would not acknowledge the disease. But in Paris, Trousseau gave the condition Addison's name, and Brown-Séquard founded experimental endocrinology after reading Addison's monograph.

In England, however, Addison had one or two staunch supporters. Jonathan Hutchinson reported further cases with post-mortem findings, and Samuel Wilks loyally unravelled the misunderstandings concerning idiopathic anæmia and Addison's disease.

Oliver Wendell Holmes, in "The Poet at the Breakfast Table" describes the following conversation between the poet and Dr. Franklin, whom he consults on account of a discoloration on the forehead.

' "The colour reminds me", said Dr. Franklin, "of what I have seen in a case of Addison's disease, Morbus Addisonii."

I said I thought the author of the *Spectator* was afflicted with a dropsy to which persons of sedentary and bibacious habits are liable.

"The author of the *Spectator*!" cried out Dr. Franklin; "I mean the celebrated Dr. Addison, the inventor, I would say, discoverer of the wonderful new disease called after him."

"And what may this valuable invention or discovery consist in?" I asked, for I was anxious to know the nature of the gift which this benefactor of the race had bestowed upon us.

"A most interesting affection, and rare too. Allow me to look closely at that discoloration once more for a moment. *Cutis aenea*—bronze skin they call it sometimes—extraordinary pigmentation; a little more to the light if you please. Ah! now I get the bronze-colouring admirably, beautifully. Would you have any objection to showing your case to the societies of medical improvement and medical observation?"

"May I ask if any vital organ is commonly involved in this interesting complaint?" I said faintly.

"Well sir", the young doctor replied, "there is an organ which is—sometimes—a little—touched I may say; a very curious and—ingenious little organ or pair of organs. Did you ever hear of the *capsulæ suprarenales*?"

"No", said I, "is it a mortal complaint?" getting nervous.

"It isn't a complaint—I mean they are not a complaint; they are two small organs, as I said, inside of you, and nobody knows what is the use of them. The most curious thing is, that when anything is the matter with them, you turn of the colour of bronze. After all I didn't mean to say I believed it Morbus Addisonii; I only thought of that when I saw the discoloration."

So he gave me a recipe which I took care to put where it could do no hurt to anybody, and I paid him his fee (which he took with the air of a man in the receipt of a great income), and said good morning.'

Comparison Between the Discovery of Addison's Disease, Gull's Disease and Cushing's Syndrome

It has always seemed to me interesting to compare the circumstances under which Addison's disease, Gull's disease and Cushing's syndrome were launched upon the medical profession.

Addison, a morose and parochial physician diffidently describing first pernicious anæmia, and then, goaded on to more spectacular publication, produced a monograph which is still a masterpiece of clinical virtuosity, accurate and even now up to date in every detail. This monograph, now one of the most famous in medical literature, was the subject of bitter controversy when it first appeared.

Gull, Napoleonic, epigrammatic extrovert, the "physician of fashion", as he once described himself, of the 1870's, who had lately been called in by Sir William Jenner to attend the Prince of Wales in his attack of typhoid fever, and had won the heartfelt thanks not only of the Nation but also of a mother who had lost her beloved husband from the same complaint: Gull, now Sir William, and one of the most famous men in England, read a paper in 1873 to the Clinical Society of London "On a cretinoid state supervening in adult life in women". The paper was brief and not very different from the usual type of communication that was constantly reported in the *Transactions* at that time. It was, however, by Sir William Gull, and that sufficed to draw attention to it. This paper contained the first description of myxœdema, and though William Ord elaborated the clinical syndrome in 1877 and called it "myxœdema" there was no doubt from the beginning that it was Gull who discovered the condition. It is, however, interesting to note that though it is quite frequently still spoken of on the Continent and in America as "Gull's disease", I found it necessary in announcing the title of a clinical lecture I was to give at Guy's Hospital last year on "Gull's Disease" to add in brackets "Myxœdema".

Cushing's syndrome was described by Harvey Cushing in 1932 in the *Bulletin of the Johns Hopkins Hospital*. He recorded 12 cases of this syndrome, and as he told me himself he travelled sometimes many hundreds of miles at short notice to be present at the post-mortem of some of the cases reported. Once again the eponym was applied by someone in another country (Bishop and Close), this time in England, and in this case it is possible that the eponym is well applied, for we still are not certain where the lesion lies, whether in the basophil cells of the pituitary, in the adrenal cortex, or whether, in some cases, there is a lesion at all. Cushing, at the time of his description of this syndrome, was the most famous neurosurgeon in the world. Whatever he might describe would instantly attract attention.

Cushing's discovery is not so very long ago. We are apt to think that Medicine has become so complicated, and so dependent on the laboratory and on team work, that no one individual can stand out as a giant among his peers in this rapidly progressing subject of endocrinology. This is surely not true. Fuller Albright, for instance, still a young man, is a prodigious giant of clinical and biochemical endocrinology, and it is my belief that the days of discovery of important and exciting syndromes have not yet passed, and that members of

this Section will continue to emulate the brilliant example of Thomas Addison, the founder of endocrinology, a hundred years ago.

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